

Calculation of complex DNA damage induced by ions

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This paper is devoted to the analysis of the complex damage of DNA irradiated by ions. The analysis and assessment of complex damage is important because cells in which it occurs are less likely to survive because the DNA repair mechanisms may not be sufficiently effective. We studied the flux of secondary electrons through the surface of nucleosomes and calculated the radial dose and the distribution of clustered damage around the ion's track. The calculated radial dose distribution is compared to simulations. The radial distribution of the complex damage is found to be different from that of the dose. Comparison with experiments may solve the question of what is more lethal for the cell, damage complexity or absorbed energy. We suggest a way to calculate the probability of cell death based on the complexity of the damage. This work is done within the framework of the phenomenon-based multiscale approach to radiation damage by ions.

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I. INTRODUCTION: MULTISCALE APPROACH TO RADIATION DAMAGE

Ion beam cancer therapy has been in a stage of booming development recently. Despite the success of this technique, a number of scientific questions on the microscopic level have not yet been resolved. This field has attracted much attention in the scientific community [1–9]. Among these is the multiscale approach to the radiation damage induced by irradiation with ions, aimed at the phenomenon-based quantitative understanding of the scenario from the incidence of an energetic ion on tissue to the cell death. This approach joins together many spatial, temporal, and energetic scales involved in this scenario. The success of this approach will provide a phenomenon-based foundation for ion-beam cancer therapy, radiation protection in space, and other applications of ion beams. The main issues addressed by the multiscale approach are ion stopping in the medium [10], production and transport of secondary electrons produced as a result of ionization and excitation of the medium [10, 11], interaction of secondary particles with biological molecules, most important being DNA [7], the analysis of induced damage, and evaluation of the probabilities of subsequent cell survival or death. This approach is interdisciplinary, since it is based on physics, chemistry, and biology. Moreover, it spans several areas within each of these disciplines.

The multiscale approach started with the analysis of ion propagation, which resulted in the description of the Bragg peak and the energy spectrum of secondary electrons [10, 11]. The practical goal of these works provided a recipe for an economical calculation of the Bragg peak position and shape. Theoretically, they concluded that

the cross section of ionization of molecules of the medium, singly-differentiated with respect to the energies of secondary electrons, is the most important physical input on this scale (the longest in distance and highest in energy). Relativistic effects play an important role in describing the position of the Bragg peak as well as the excitation channel in inelastic interactions [10]. The effect of charge transfer and projectile scattering influence the shape of the Bragg peak [10]. The effects of nuclear fragmentation happening in the events of projectile collisions with the nuclei of the medium are also important on this scale.

The next scale in energy and space is related to the transport of the secondary particles, which has been considered in Refs. [7, 12], but it may still be revisited. The results of these analyses give the spatial distributions of secondary particles as well as an accurate radial dose distribution.

The goal of the analysis of DNA damage mechanisms is to obtain the effective cross sections for the dominant processes, which should be taken into account in order to calculate the probability of different lesions caused by different effects. The above three stages of processes, represent not only different spatial scales, but also different time scales, ranging from the 10^{-21} to 10^{-5} seconds. The aim of the physical part of the analysis is the calculation of the spatial distribution of primary DNA damage, including the degree of complexity of this damage. Then, the repair and other biological effects can be included and thus the relative biological effectiveness (RBE) can be calculated. The RBE [1, 5] is one of the key integral characteristics of the effect of ions compared to that of photons. This ratio compares the doses of different projectiles leading to the same biological effect.

Traditionally, the radial dose, calculated in Ref. [12], is related to the radial distribution of damage. However, this does not include the complexity of damage, which may not be directly related to the dose. It is still not clear how to relate the dose with the complexity of the damage. This work is a step in this direction.

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Finally, the analysis of the possibility of thermo-mechanical damage pathways has been started in Refs. [10] and has further advanced in Refs. [13, 14]. This idea stems from the fact that the energy lost by an ion is transferred to the tissue's internal degrees of freedom and then becomes thermalized. We analyzed this transition in Ref. [13] and used it as an initial condition for hydrodynamic expansion described by a cylindrical shock wave in Ref. [14]. These works predict a rapid rise of temperature and pressure in the vicinity of the track. Then, when the expansion starts, the pressure is high on the wave front, but quickly drops in the wake of the wave causing large pressure gradients, and therefore, strong forces, which may rupture bonds of biomolecules that may be located within several nm of the track. It was shown that these forces can be strong enough to break covalent bonds (more than 10 nN) but act only for a very short time. An estimate of work done by this force, based on Ref. [14], is several eV, but still more research is needed in order to investigate whether this represents a separate mechanism of damage. This effect may also be important in defining the conditions of the medium in which the other known radiation damage mechanisms (e.g., electron attachment or free radical attack on DNA) take place.

This work is devoted to the calculation of damage complexity and its distribution. This is an important stage in the multiscale approach, since it is closely related to the probability of cell death as a result of damage [15–19]. Damage complexity is one of the defining factors in calculating RBE.

In Sec. II we define the complex damage and present a way to quantify it. In Sec. IIA we calculate the fluence of secondary electrons as a step in the assessment of complex damage. In Sec. IIB we calculate the radial dose distribution and give an example of a calculation of the complex damage on that basis.

II. DISTRIBUTIONS OF THE COMPLEX DAMAGE

Complex damage is defined as the number of DNA lesions, such as double strand breaks (DSB), single strand breaks, abasic sites, damaged bases, etc., that occur within about two helical turns of a DNA molecule so that, when repair mechanisms are engaged, they treat a cluster of several of these lesions as a single damage site [15–17]. In Ref. [9], the complexity of DNA damage has been quantified by defining a cluster of damage as a damaged portion of a DNA molecule by several independent agents, such as secondary electrons, holes, or radicals.

In humans, DNA molecules are by and large located in cell nuclei, where they are organized with proteins into chromatin fibres. The main structural unit of chromatin fibres is a nucleosome [20]. A nucleosome core particle consists of about a 146-bp section of a DNA molecule

wrapped around a cylindrical aggregate of eight histone proteins (histone octamer).

A. Damage complexity distribution from the random walk approach

In Ref. [7], we studied the transport of secondary electrons to a given DNA convolution. This study led to the calculation of the radial distribution of DSBs with respect to the ion track. This calculation was limited by only considering secondary electrons to be the agents of DNA lesions. Nevertheless, this allowed us to make an estimation of the number of DSBs produced by ions per unit length of track in the vicinity of the Bragg peak. The results obtained in that work were in reasonable agreement with the experimental data [21]. The approach of Ref. [7] can be used for calculating the radial distribution of damage complexity.

Let us choose two adjacent convolutions of a DNA molecule as a target. Then, the average number of lesions per this segment of DNA, N , is given by a product of the probability of inducing damage by a secondary particle on impact, Γ , by the fluence through the target. Alternatively, it is given by the same probability multiplied by the volume of the segment and by the number density of agents. The probability of complex damage is then a Poisson distribution $P(N, \nu)$,

$$P(\rho, \nu) = \exp(-N(\rho)) \frac{N(\rho)^\nu}{\nu!}, \quad (1)$$

where ν is the degree of complexity [9]. In Eq.(1), N is written as a function of ρ , the distance of the segment from the track. Our goal is to calculate the radial distribution of complex damage with respect to the ion track in the simplest case, when all agents are equivalent, keeping the probability Γ as a parameter. In this paper, we limit secondary particles to secondary electrons. A further development will include transport of secondary particles including chemical reactions and more details of their distributions.

In this section, we calculate the fluence of the secondary electrons, through the DNA segment. In order to do this, we consider their diffusion from the place of their origin as was done in Ref. [7]. We assume that the diffusion of the secondary electrons is cylindrically symmetric with respect to the ion's track and calculate the number of electrons, which hit two adjacent convolutions of a DNA molecule. The cylindrical diffusion in the vicinity of the Bragg peak can be justified by the fact that during the time that it takes secondary electrons to diffuse by about 10 nm, the projectile moves a distance of about 1 μm [14]. The linear energy transfer (LET) along this distance, described by the coordinate ζ , remains nearly constant, as well as the production of secondary particles per unit length $\frac{dN}{d\zeta}$; therefore, the latter is independent of ζ . This number of secondary electrons produced per

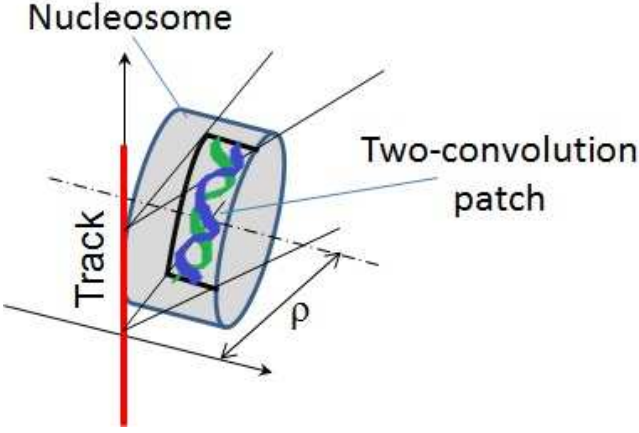


FIG. 1: Geometry of the problem. Secondary electrons radially diffuse from the ion's track and interact with a section of DNA molecule wrapped around a histone octamer.

one nm of the ion's track is taken to be equal to 20, which corresponds to the average number of ionizations per one nm of ion's track in the vicinity of the Bragg peak [7, 10].

Naturally, we expect the largest damage occurring when the incident ion passes through a nucleosome. Therefore, in this paper, we calculate the complex damage that takes place in two consecutive convolutions of a DNA molecule on the surface of a nucleosome situated outside the ion's track (neglecting the stretches of linker DNA connecting nucleosomes). In what follows, a nucleosome is represented by a cylinder of radius 5.75 nm and height of 6 nm and the target section of a DNA molecule is a rectangular patch (7.2nm × 2.3nm) of its surface, as shown in Fig. 1.

In order to calculate the fluence, we consider the rate of secondary electrons, dN_A/dt , at the time t , passing through the patch $d\vec{A}$, located at a distance ρ from the track. According to Ref. [22], for a cylindrically symmetric random walk, it is given by the expression

$$\begin{aligned} \frac{dN_A(\vec{r}, t)}{dt} &= d\vec{A} \cdot D \nabla P(t, \rho) \frac{dN}{d\zeta} \\ &= d\vec{A} \cdot D \mathbf{n}_\rho \frac{\partial P(t, \rho)}{\partial \rho} \frac{dN}{d\zeta}, \end{aligned} \quad (2)$$

where $D = \bar{v}l/4$ is the diffusion coefficient, l is the elastic mean free path of electrons in the medium¹, \bar{v} is the speed of the electron, \mathbf{n}_ρ is a unit vector in the radial direction from the track, and

$$P(t, \rho) = \frac{1}{\pi \bar{v} t l} \exp\left(-\frac{\rho^2}{\bar{v} t l}\right) \quad (3)$$

¹ In two dimensions, l is a product of the mean free path in three dimensions multiplied by the factor of $\sqrt{2/3}$.

is the probability density to observe a randomly walking electron at a time t and a distance ρ from the track. Eventually we are going to integrate Eq. (2) over both, the time (to get the total number of electrons incident on the patch $d\vec{A}$) and $d\vec{A}$ (in order to calculate the total number of electrons incident on a two-twist-segment of a DNA molecule). Before we do this, we need to somewhat modify expressions (2) and (3).

First, the time dependence can be translated to the dependence on number of steps, k , using $\bar{v}t = kl$ and $\bar{v}dt = ldk$.

Second, there is a probability that the electron interacts with a molecule inelastically, loses energy and drops off from a random walk. In order to account for such a subtraction, we introduce an attenuation factor $\epsilon(k)$. In Ref. [7], we used

$$\epsilon(k) = \gamma \exp(-\gamma k), \quad (4)$$

where γ is a constant, proportional to the ratio of mean free paths between inelastic and elastic collisions. This expression is physically motivated, but it does not take into account the energy dependence of mean free paths and their ratio. In this paper, we will keep the elastic mean free path l energy-independent and equal to 1 nm [12], while we will use the attenuation given by

$$\epsilon(k) = \exp(\alpha \exp(-k^\beta)). \quad (5)$$

This expression with constants $\alpha = 60$ and $\beta = 0.055$ appears as a result of fitting the radial dose distribution derived from a model of secondary electron transport to that obtained using Monte Carlo simulations [23]. This model assumes a random walk of electrons with a constant mean free path, i.e., the same used by us in this section. Expression (5), with a modified dependence on k , implicitly introduces the dependence of the attenuation on energy. The attenuation according Eq. (5) is steeper than that according to Eq. (4) for small k . This means that electrons with higher energy tend to lose it in inelastic collisions more quickly than those with smaller energies and the attenuation at large k is much smaller. We will return to this parametrization in the following section.

Now we can rewrite Eq. (2), substituting (3), including the attenuation, and switching from variable t to k as

$$dN_A(\vec{r}, k) = dk d\vec{A} \cdot \mathbf{n}_\rho \frac{\rho}{2\pi k^2 l^2} \exp\left(-\frac{\rho^2}{kl^2}\right) \epsilon(k) \frac{dN}{d\zeta} \quad (6)$$

and integrate it over the target part of surface of the cylinder, representing a nucleosome. The results of integration (6) over time and the area of the patch are shown in Fig. 2. As expected, this number decreases with distance ρ from the track.

If we multiply this number, N_A , by the probability, Γ , of producing a lesion in a DNA molecule, uniformly distributed on the surface of the nucleosome, we obtain the dependence of the number of lesions on the distance

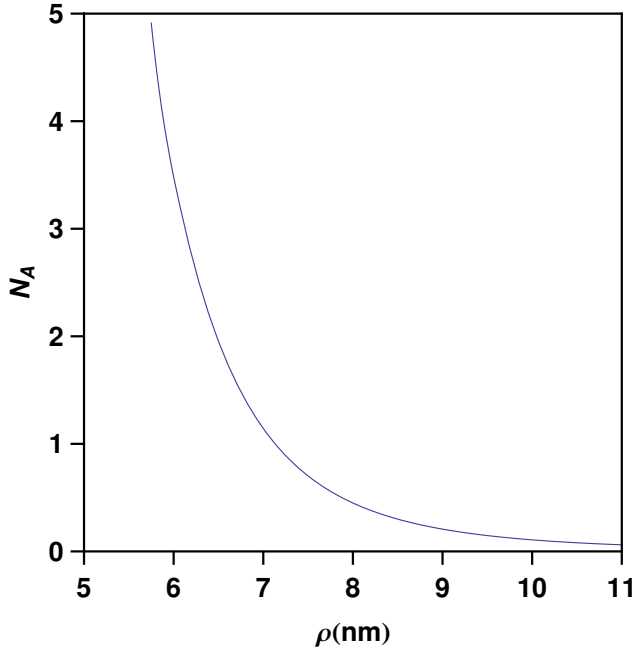


FIG. 2: Number of secondary electrons diffused through a two-convolution segment of DNA molecule on the surface of a nucleosome in the vicinity of the ion's track, plotted as a function of the distance ρ of nucleosome from the track. The calculation is done with a use of the attenuation function given by Eq. (5).

from the track. Then, Eq. (1) can be used, with

$$N(\rho) = \Gamma N_A(\rho) \quad (7)$$

to calculate the radial distributions of probabilities of clusters of lesions.

This number has to be corrected by to include further ionizations and holes, which also play a role in the damage. Holes may recombine producing Auger electrons, capable of inducing lesions to DNA [24]. Before these corrections are made, these calculations remain qualitative. When the transport properties of electrons and other secondary particles in the medium are known and $N(\rho)$ is calculated more definitely, the approach to the calculation of the clustered damage, described above, can be useful.

In addition to this calculation, it is possible to compute similar probabilities for cases when the track passes through the nucleosome; but this would require calculating the transport of secondary electrons through a histone and knowledge of the elastic and inelastic cross sections of electrons in this medium. Recent calculations indicate a 20% higher stopping power of DNA compared to liquid water [25]. We will postpone these calculations until another time. However, it may be worth mentioning that the clustered damage of a histone may also deserve attention in regard to cell damage.

The calculation of the number of secondary electrons

passing through a patch on a nucleosome presented in this section is important for several reasons. First, it can be compared with Monte Carlo simulations done for the purposes of nanodosimetry [26]. Second, it will be possible to compare this dependence (correspondingly modified) with dosimetric experiments [27, 28]. At this point, it is possible to use the dependence shown in Fig. 2 for the calculation of the complex damage (using additional parameters); however, in this paper, we choose to use the radial dose distribution to demonstrate a calculation of complex damage. At this moment, the latter approach allows for more checkpoints and we describe it in the next section.

B. Derivation of damage complexity from the radial dose distribution

As was shown in Ref. [12], the radial number density distribution of secondary electrons that lost energy and became thermalized or bound is related to the radial dose. Here, we revisit the calculation of the radial dose and infer the secondary particle distribution, with the complexity distribution following from that.

Let us assume that all secondary electrons start from the ion's track and propagate via random walk in two dimensions; this corresponds to the cylindrically symmetric propagation (neglecting some fast δ -electrons). Then, according to Eq. (3), rewritten in terms of k , the probability to find a secondary particle in a cylindrical layer of unit length between ρ and $\rho + d\rho$ after k random steps is $\frac{dN_s}{d\zeta} P(k, \rho) 2\pi\rho d\rho$. This probability is normalized to $\frac{dN_s}{d\zeta}$, for any number of steps k if we integrate over $d\rho$ from 0 to infinity. The normalization does not change if we include the attenuation $\epsilon(k)$ due to inelastic processes and introduce a distribution over k . Transferring from the sum to the integral, appropriate for large k , this can be written as

$$\int_1^\infty \int_0^\infty P(k, \rho) \epsilon(k) 2\pi\rho d\rho dk = 1. \quad (8)$$

Then the density of the particles, which lost energy within the cylindrical layer of a unit length between ρ and $\rho + d\rho$ can be obtained by dividing the integrand of Eq. (8) by the volume of this shell of a unit length, i.e., $2\pi\rho d\rho$ and the radial dose $\mathcal{D}(\rho)$ can be obtained by multiplication of this density by the average energy per particle $\bar{W} = 45$ eV [10]:

$$\mathcal{D}(\rho) = \bar{W} \frac{dN_s}{d\zeta} \int_1^\infty P(k, \rho) \epsilon(k) dk. \quad (9)$$

This dose is normalized by the LET:

$$\int_0^\infty \mathcal{D}(\rho) 2\pi\rho d\rho = LET. \quad (10)$$

However, the radial dose distribution calculated using

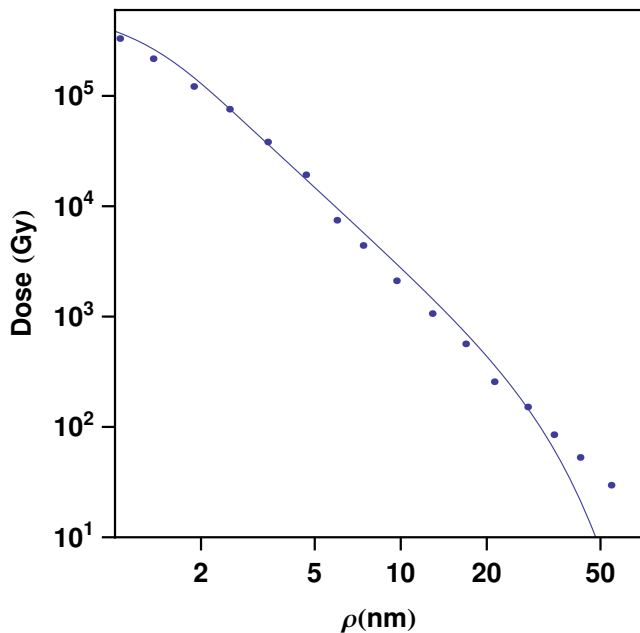


FIG. 3: Comparison of the calculated radial dose (line), Eq. (9) with the simulated in Ref. [23] (dots) for 25 MeV/u carbon ions.

Eq. (9) with the attenuation, defined by Eq. (4), does not agree with simulations of, e.g., Ref. [23]. The reason for this is that in Eq. (4) we have assumed energy-independent attenuation. According to, e.g., Ref. [29], both elastic and inelastic mean free paths are energy dependent. Moreover, as has been pointed out in Ref. [7], the dependence of ranges of low-energy electrons in liquid water on energy, discussed in Ref. [30], indicates that the attenuation steeply decreases as the energy of the electron decreases (after several inelastic collisions). This can be taken into account by parametrizing the attenuation as a function of k so that the dose calculated using Eq. (9) agrees with experiments and simulations. In this work, we have found that the dose, calculated using Eq. (9) with attenuation defined by (5) with parameters α and β given above² is in reasonable agreement with that simulated in Ref. [23]. This comparison is shown in Fig. 3.

The simulation, done in Ref. [23] corresponds to 25-MeV carbon ions with $LET = 60$ eV/nm. This is about 4 mm away from the Bragg peak, where $LET = 900$ eV/nm. Therefore we recalculated the same dose using the procedure described above for 0.3-MeV/u carbon ions with a $LET = 900$ eV/nm. The result is presented in Fig. 4. This distribution can be compared to the experimental measurements of the radial dose distribution; however, at this moment, such data are not available for

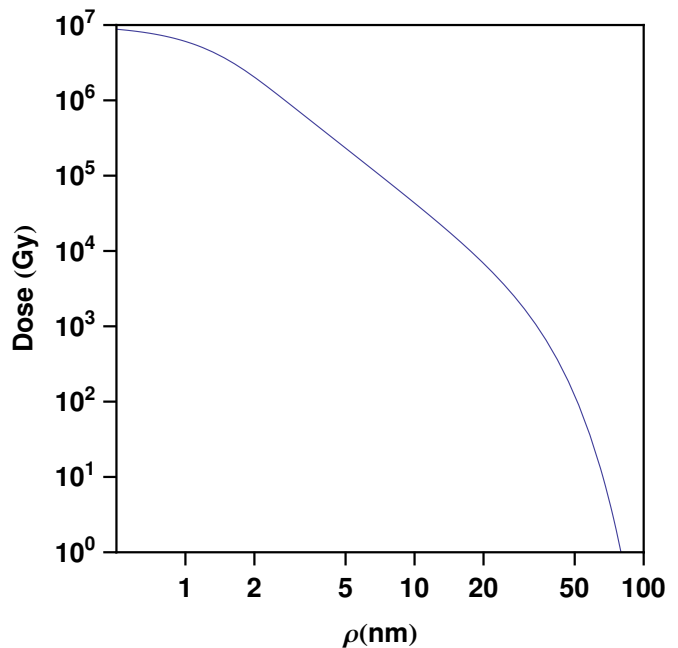


FIG. 4: Calculated radial dose distribution for $LET=0.9$ keV/nm.

such a LET .

Using this dose distribution around a single ion's track, we can calculate the distribution of clusters of DNA damage. In order to do this, we have to divide the expression (9) for the dose by \bar{W} , and obtain the radial distribution of the density of inelastically interacting secondary electrons. If then we multiply that by the effective volume of the target segment DNA and the probability of producing a lesion Γ , we will obtain $N(\rho)$. Then, we can calculate the radial distribution of complex damage using Eq. (1). This will only be correct if $N(\rho)$ does not significantly change over this volume.

If we assume that the effects of varying $N(\rho)$ on the size of some effective volume can be neglected, then we can calculate the radial distribution P_c of clusters for a given ν . An example of such dependencies for a volume of 40 nm^3 (corresponding to the volume occupied by two convolutions of DNA molecule) and $\Gamma = 0.1$ of two- and three-lesion clusters, are shown in Fig. 5.

These distributions give us an opportunity to verify the significance of clusterization. If, e.g., all clusters containing three and higher lesions are lethal for the cell, we can add up their probabilities and plot the dependence of the probability of cell death, P_d , on the distance from the track. These dependencies for $\Gamma = 0.1$ and $\Gamma = 0.3$ are shown in Fig. 6. This figure indicates that if the clusters of three and more lesions per nucleosome are indeed lethal, then the effective distance from the track on which the cells are killed is less than 1.5 nm for $\Gamma = 0.1$ and it exceeds 2 nm for $\Gamma = 0.3$. Hence, in the first case, it is essential that the ion passes through a nucleosome in order

² Expression (5) has to be divided by $\int \epsilon(k)dk$ for normalization.

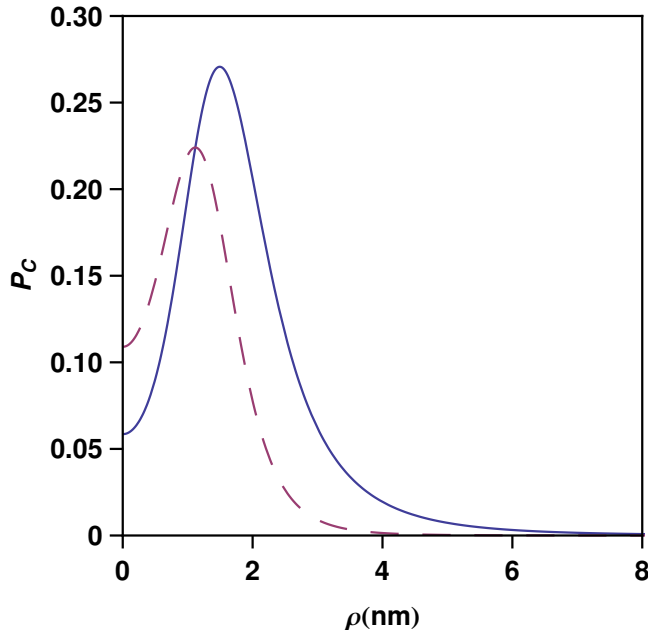


FIG. 5: Radial distribution of clusters of two (solid line) and clusters of three lesions (dashed line) for $\Gamma = 0.1$.

to kill the cell, while in the second, a nucleosome can be at a distance and still be severely damaged. This analysis opens several fields for comparison with experiments: the dependence of lethality on the radial distance from the track and on the size of clusters of lesions for biophysics and the radial dependence of dose and cluster damage distribution for nano-dosimetry. The radial scale in Fig. 6 is shorter than 10 nm. Even though, this size is about 1000 times smaller (for glial cells) than that of the cell's nucleus [7]; it plays a significant role in calculations of the probability of cell death and will be critical for the comparisons with nano-dosimetric data [26–28, 31].

If we keep the assumption that three and higher order lesion clusters are lethal to the cell, then we can plot the dependence of $1 - P_d$, similar to the probability of cell survival, on the radial dose. This dependence is presented in Fig. 7 and this can also be compared with experiments. The scale on the abscissa for the radial dose is indeed in MGy. This is by a factor of 10^6 larger than that in typical cell survival curves [32], where the dose is absolute, i.e., planar-integrated per ion and distributed for the whole beam. A typical spatial distance between the ion tracks is larger than 350 nm.³ Therefore, the volume per one nm of the ion's track is at least 10^5 nm^3 . This makes the average integral dose at the Bragg peak of a single carbon ion about $7 \times 10^{-3} \text{ eV nm}^{-3} = 110 \text{ Gy}$. This dose has to be averaged once again when one considers the

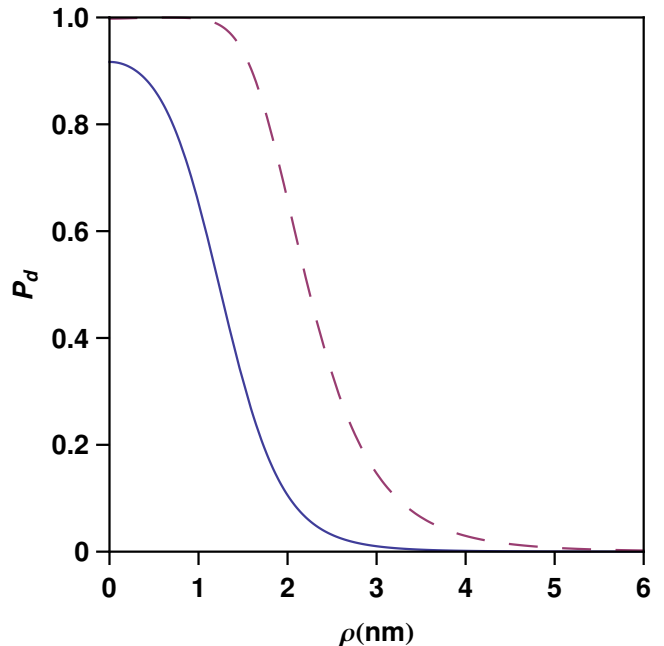


FIG. 6: Radial distribution of clusters of three and more lesions, deemed proportional to the probability of cell death. The solid curve corresponds to $\Gamma = 0.1$ and the dashed one to $\Gamma = 0.3$.

whole ion beam. This brings another factor of the order of 0.1, which reduces the maximum dose to 10-15 Gy. The absolute dose is important for treatment planning, but here we are interested in a more detailed description and the radial, not averaged dose, is more relevant for this purpose. This is why we presented the dependence of a probability cell survival on the local radial dose. Below we show how to do a planar integration and give an example of an estimate.

The radial distributions of clustered damage probabilities can be integrated over the radius in order to obtain the probability of lethal damage per unit length. This is relevant for current experiments. When experimentalists study foci, which reveal the efforts of proteins to fix damaged DNA, they observe that the foci are very large, compared to the scale of the radial distribution of the dose. The experimentalists can measure the linear density of clusters along the track and hypothesize about the number of certain lesions, such as DSB, per unit length [33].

In order to obtain the longitudinal distributions of clusters, we have to introduce the density of the distribution of nucleosomes with respect to the ion track, $\eta(\rho)$. Then, we can integrate the radial-dependent probability of the complex damage given by Eq. (1) (for appropriate $N(\rho)$ dependence) with this density distribution:

$$P(\nu) = \int_0^\infty \exp(-N(\rho)) \frac{N(\rho)^\nu}{\nu!} \eta(\rho) 2\pi\rho d\rho. \quad (11)$$

³ According to the beam data [1].

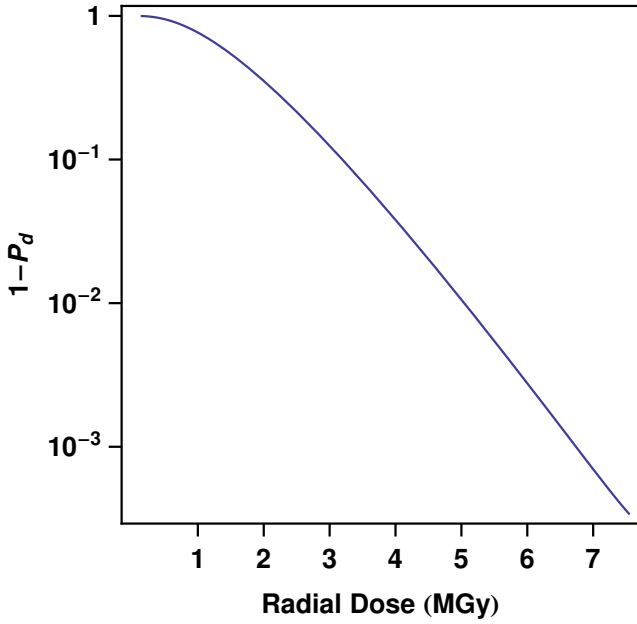


FIG. 7: The dependence of $1 - P_d$, similar to cell survival rate (dimensionless) on the local radial dose per ion with $\Gamma = 0.3$.

This gives the number of clusters of ν lesions per nm, which can be compared with the nano-dosimetric experiments [26–28, 31] and can give still another relation for unknown parameters such as Γ and the dependence of lethality of damage on the order of cluster ν .

The density of the distribution of nucleosomes, $\eta(\rho)$, depends on the structure of packing nucleosomes in fibers. If we consider a section of a cylindrical fiber of tightly packed nucleosomes [20] to be parallel to the track 1 nm away from its surface, then an estimate made with the above assumptions producing the maximal effect of damage complexity, predicts about 3 complex damage sites (with $\nu > 2$) per 10 nm of a carbon ion's track.

III. CONCLUSIONS

The multiscale approach was designed in order to understand the mechanisms that make the ion-beam therapy effective. This includes the understanding of what is truly different between different therapies. It is widely accepted that the high-LET radiation brings about high dose in the desired location. However, it is not yet clear whether the dose entirely accounts for all biological consequences. Namely, how different are the dose and complexity distributions and which of them is responsible for the cell death? This paper tackled these questions and, although more experiments are needed to confirm them, the principle framework of the problem has been set up.

The main accomplishments of this paper are the calculation of the radial dose distribution (comparable with that obtained by simulations), derivation of the radial distribution of secondary electrons from the radial dose distribution, and the calculation of the radial distributions of different clusters of lesions. On the basis of these distributions we developed models for calculations of dependencies of the probabilities of cell death as a result of complex damage of DNA on the distance from the ion's track and along the track. These calculations may be very practical and we hope that it will be explored by experimentalists in nano-dosimetry as well as by biophysicists. The main principle point in our approach to damage complexity is that it can be described by a spatial distribution and compared to the radial dose distribution and the distribution of killed cells.

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